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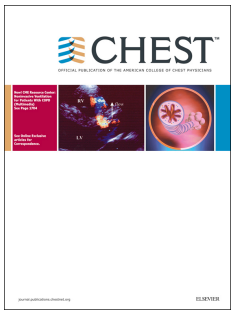
Published in:
Chest

DOI (link to publication from Publisher):
10.1016/j.chest.2019.11.025

Publication date:
2020

Document Version
Version created as part of publication process; publisher's layout; not normally made publicly available

Journal Pre-proof



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PII: S0012-3692(19)34383-1

DOI: https://doi.org/10.1016/j.chest.2019.11.025

Reference: CHEST 2762

To appear in: *CHEST*

Received Date: 23 June 2019

Revised Date: 19 October 2019

Accepted Date: 9 November 2019

Please cite this article as: Chao TF, Chiang CE, Liao JN, Chen TJ, Lip GYH, Chen SA, Comparing the Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants and Warfarin in the Elderly Asian Patients with Atrial Fibrillation: A Nationwide Cohort Study, *CHEST* (2020), doi: https://doi.org/10.1016/j.chest.2019.11.025.

Comparing the Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants and Warfarin in the Elderly Asian Patients with Atrial Fibrillation: A Nationwide Cohort Study

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Running title: NOACs vs warfarin in the elderly

Total word count: 2,890; **Conflict of interest:** None

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Abstract

Background: Stroke prevention in elderly patients with atrial fibrillation (AF) can be challenging, requiring a balance between thromboembolism prevention and serious bleeding. Comparisons of non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in the elderly, at different age strata (age 65-74, 75-89, ≥90) in the daily practice have not been well described, particularly in Asians. We aimed to assess the clinical outcomes of NOACs compared to warfarin for stroke prevention in elderly patients with AF.

Methods: From 2012 to 2015, 64,169 AF patients aged ≥ 65 years who received at least 1 NOAC (dabigatran, rivaroxaban, or apixaban) or warfarin prescription were identified from the Taiwan National Health Insurance Research Database. The risks of ischemic stroke, intra-cranial hemorrhage (ICH), major bleeding, mortality and composite adverse events were compared between NOACs and warfarin in all patients age ≥65 and specifically, with different age strata; that is 65-74 years, 75-89 years and ≥90 years.

Results: Overall NOACs were associated with a significantly lower risk of ischemic stroke (adjusted hazard ratio [aHR] 0.869, 95% confidence interval [CI] 0.812-0.931), ICH (aHR 0.524, 95%CI 0.456-0.601), major bleeding (aHR 0.824, 95%CI 0.776-0.875), mortality (aHR 0.511, 95%CI 0.491-0.532) and composite adverse events (aHR 0.646, 95%CI 0.625-0.667) compared to warfarin. There was heterogeneity in treatment effect for NOACs versus warfarin in different age strata, but the results still favored NOACs even among the very elderly (≥ 90 years). The results were generally consistent with propensity matching analysis. The absolute risk difference and reductions in ICH and composite adverse events with NOAC use were even greater among the elderly compared to warfarin.

Conclusions: Compared to warfarin, NOACs were associated with a significantly lower risk of adverse events, with heterogeneity in treatment effects among different age strata. Overall,

the clear safety signal in favor of NOACs over warfarin was evident irrespective of age strata, being most marked in the most elderly.

Key words: atrial fibrillation, NOACs, warfarin, stroke, mortality, bleeding

Introduction

The incidence and prevalence of atrial fibrillation (AF) significantly increase with age,[1] and stroke prevention is the cornerstone for the management of elderly AF patients given their high risk of ischemic stroke.[2] Age is a powerful driver of stroke risk but thromboprophylaxis in the elderly is challenging, requiring a balance between thromboembolism prevention and serious bleeding.[3]

Prescription rates of OACs are generally suboptimal among the elderly, for example, being only 36% for patients aged ≥85 years in a general practice cohort from the United Kingdom.[4] In our recent report, only 3.9% of newly-diagnosed Asian AF patients aged ≥90 years were treated with warfarin in the Taiwan nationwide cohort.[5] Several reasons could partly explain the underuse of OACs among the elderly, such as the relative lacking of evidence, the physician's concern of bleeding and an inability of some patients to cope with warfarin monitoring.

The introduction of the non-vitamin K antagonist OACs (NOACs) have provided an equally effective, safer and more convenient choice than warfarin,[6] NOACs may overcome some of the reasons of the underuse of warfarin in the elderly. Although no randomized trial has specifically randomized elderly adults to compare NOACs with warfarin, sub-analyses of four landmark NOACs trials (RELY, ROCEKT-AF, ARISTOTLE, and ENGAGE AF-TIMI 48) in different age strata have been published.[7-10] The results of these studies have shown that the benefits of NOACs versus warfarin were consistent in patients with AF regardless of age. In these studies, "the elderly" were defined as patients aged ≥ 75 years, and data about the comparisons of NOACs and warfarin in even older patients (e.g. age ≥ 90 years) were limited, given that such patients were under-represented in the clinical trials.

In this nationwide cohort study, we aimed to compare the risks of ischemic stroke, intracranial hemorrhage (ICH), major bleeding and mortality among AF patients aged ≥ 65 years treated with NOACs and warfarin. Second, these patients were stratified into different age strata (age 65-74, 75-89 and ≥90 years). We hypothesized that the benefits of NOACs were maintained and possibly even greater in the elderly.

Methods

This study used the "National Health Insurance Research Database (NHIRD)" provided by Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW), Taiwan. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. NHIRD consists of detailed health care data from >23 million enrollees, representing >99% of Taiwan's population. In this cohort dataset, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously. The descriptions about Taiwan NHIRD have been reported in our previous studies.[11-16]

Study cohort and study design

From January 1, 2012 to December 31, 2015, a total of 324,825 AF patients aged ≥ 20 were identified. AF was diagnosed using the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification (ICD-9-CM) codes (427.31). To ensure the accuracy of diagnosis, we defined patients with AF only when it was a discharge diagnosis or confirmed for at least 2 times in the outpatient department. The diagnostic accuracy of AF using this definition in NHIRD has been validated previously.[17] Among the study population, there were 64,169 AF patients aged ≥ 65 years who received at least 1 NOAC (dabigatran, rivaroxaban, or apixaban) or warfarin prescription. The mean drug adherence rate of OACs, calculated based on proportion of days covered with OACs during the entire follow-up period for each patient, was 69%. The risks of ischemic stroke, ICH, major bleeding and mortality were compared between NOACs and warfarin in all patients age ≥65 and specifically, with

different age strata; that is 65-74 years, 75-89 years and ≥90 years. The flowchart of study design is shown in Figure 1.

Calculation of scores and clinical outcomes

The CHA_2DS_2-VASc score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, history of hypertension, diabetes, congestive heart failure, vascular disease (myocardial infarction or peripheral artery disease), and female gender, and 2 points each for a history of a stroke, transient ischemic attack (TIA), or age ≥ 75 years.[18] The HAS-BLED score was calculated by assigning 1 point each for hypertension, abnormal renal or liver function, stroke, bleeding history, age 65 years or older, and antiplatelet drug or alcohol use.[19] Since the information of international normalized ratio (INR) of warfarin was not available in the Taiwan registry database, the component of "labile INR," was excluded from the HAS-BLED score in the present study, consistent with prior registry studies. Also, abnormal renal and liver function were defined by the ICD-9-CM codes rather than laboratory data.

We analyzed the risks of several clinical events, including ischemic stroke, ICH, major bleeding, all-cause mortality and composite adverse events (ischemic stroke or ICH or major bleeding or all-cause mortality). Ischemic stroke was diagnosed using ICD-9-CM codes, with concomitant imaging studies of the brain, including computed tomography or magnetic resonance imaging. The accuracy of diagnosis of ischemic stroke in Taiwan's NHIRD has been reported to be around 94%.[20] Another validation study also demonstrated that the diagnostic accuracy of ischemic stroke in NHIRD was high, with the positive predictive value and sensitivity of 88.4% and 97.3%, respectively.[21] The safety endpoint was the occurrence of ICH necessitating admissions to intensive care units. Major bleeding was

defined as ICH or bleeding from gastrointestinal or genitourinary or respiratory tract requiring hospitalization.

Propensity match analysis

We performed propensity score–matched analyses of NOACs versus warfarin among whole study population and patients at each age strata. We calculated propensity scores for the likelihoods of receiving NOACs compared to warfarin by multivariate logistic regression analyses, conditional on all baseline covariates listed in Table 1. The results of the propensity score models about the probabilities of the use of NOACs are shown in Supplemental Table 1, Supplemental Table 2, Supplemental Table 3 and Supplemental Table 4. After that, we matched patients in the warfarin group to those in the NOACs group with a 1:1 ratio on the basis of the closest propensity score for the use of NOACs within a threshold of ±0.01 using the greedy algorithm.

Statistical analysis

Data are presented as the mean value (standard deviation [SD]) for continuous variables and proportions for categorical variables. The differences between normally distributed continuous values were assessed using an unpaired 2-tailed t test. The differences between nominal variables were compared by Chi-square test. The incidences of ischemic stroke, ICH, major bleeding, all-cause mortality and composite adverse events were calculated from dividing the number of event by person-time at risk. The risk of adverse events was assessed using the Cox regression analysis. The proportional hazards assumption was tested using Schoenfeld residual test which showed no non-proportionality. The cumulative incidence curves of adverse events for patients receiving NOACs or warfarin in different age strata were plotted via the Kaplan-Meier method, with statistical significance examined by the log-

rank test. Absolute risk differences of ICH and composite adverse events with NOACs versus warfarin in different age strata were calculated according to the crude event rates. The All statistical significances were set at a $p < 0.05$.

The present study was approved by the Institutional Review Board (IRB) at Taipei Veterans General Hospital (2016-03-002AC and 2019-10-002AC), Taipei, Taiwan and the informed consent of study subject was waived.

Results

Clinical characteristics of the study population are shown in Table 1. Patients on NOACs tended to be older and male, with more prevalent hypertension, prior stroke/TIA and hyperlipidemia, with less prevalent heart failure, vascular disease, abnormal renal function, anemia and concomitant antiplatelet drugs. Mean CHA_2DS_2-VASc score was lower and HAS-BLED score higher in warfarin users compared to NOAC users (Table 1). Similar trends were seen in clinical characteristics of study patients taking NOAC or warfarin, stratified by different age categories, as shown in Table 2.

Propensity score models for the use of NOACs are shown in Supplemental Tables 1-4. Increased probabilities of the use of NOACs amongst all patients were evident for increasing age, males, hypertension, diabetes, stroke/TIA, hyperlipidemia, abnormal liver function and history of bleeding; with less NOAC use for heart failure, vascular disease, abnormal renal function, anemia and concomitant use of antiplatelet drugs. Broadly similar trends were seen when stratified by different age categories.

Crude event rates (%/year) of patients in different age strata are shown in Figure 2. As expected, ischemic stroke, ICH, major bleeding, mortality and adverse events increased with increasing age. The relative risk of events of patients treated with NOACs compared to warfarin are shown in Figure 3. Overall NOACs were associated with significantly lower risks of ischemic stroke (adjusted hazard ratio [aHR] 0.869, 95%CI 0.812-0.931), ICH (aHR 0.524, 95%CI 0.456-0.601), major bleeding (aHR 0.824, 95%CI 0.776-0.875), mortality (aHR 0.511, 95%CI 0.491-0.532) and adverse events (aHR 0.646, 95%CI 0.625-0.667) after the adjustments for variables with a p value < 0.05 between 2 groups in Table 1.

For ischemic stroke, there was heterogeneity in treatment effect for NOACs vs warfarin, with statistically significant reduction only evident in the age 75-89 category (p

interaction [p_{int}], <0.001). For ICH and composite adverse events, NOACs were significantly better compared to warfarin, especially in the very elderly for ICH (p_{int} <0.001). For major bleeding, there was also significant heterogeneity, particularly in the very elderly (age ≥90) subgroup, where there was no statistical difference for NOACs compared to warfarin (p_{int} <0.001).

The cumulative incidence curves of clinical events by age strata are shown in Figure 4. As expected, older patients were at higher risks of ischemic stroke, ICH, major bleeding and mortality, with generally better benefits with NOACs versus warfarin. Importantly, the risk of ICH was even lower for the very elderly patients treated with NOACs compared to younger patients treated with warfarin.

Figure 5A shows the annual event rates of ICH of patients treated with warfarin and NOACs from the young to old age strata at an interval of 5 years, and the absolute risk difference of ICH between warfarin and NOACs was even more evident in the elderly. ICH absolute event reductions (per 1000 patient-years) with NOACs compared to warfarin was even larger among the elderly (Figure 5B). Similar patterns were also noted for overall adverse events (Figure 6A and Figure 6B).

Propensity matched analysis

Clinical characteristics of the whole cohort and by age strata following propensity score matching are provided in Supplemental Table 5 and Supplemental Table 6, respectively. Baseline characteristics and propensity scores were not significantly different between patients treated with warfarin or NOACs after the matching. Consistent with the overall main analysis, NOACs were associated with significantly lower ischemic stroke, ICH, major bleeding, mortality and adverse events in the propensity matched analysis (Supplemental Figure 1). The observations by age strata in the propensity matched analysis were generally

consistent with the overall analysis (Supplemental Figure 1).

Discussion

In this paper, our principal findings are as follows: (i) NOACs were associated with a significantly lower risk of ischemic stroke, ICH, major bleeding, mortality and overall adverse events compared to warfarin among AF patients aged ≥ 65 years; (ii) there was heterogeneity in treatment effect for NOACs versus warfarin in different age strata, but the results still favored NOACs even among the very elderly (≥ 90 years); and (iii) compared to warfarin, the absolute risk differences and reduction of event numbers for ICH and composite adverse events with NOAC users were even greater among the elderly.

The NOACs have changed the landscape for stroke prevention in AF,[2,22] although regional differences in prescribing are evident.[23] Nevertheless, NOACs are the preferred OAC option in guidelines.[3,24,25] In Taiwan, every NOAC was fully reimbursed by Taiwan NHI program, mainly following the inclusion criteria of RE-LY trial, and could be prescribed as the first-line therapy for stroke prevention without trying warfarin first. Even though, OACs were only prescribed in 25.8% of patients aged ≥ 65 years in the present study, which was much lower than that reported from GARFIELD-AF (71.1%) and GLORIA-AF (60.7%) registries.[26,27] More efforts are necessary to improve the prescription rate of OACs in the daily practice in Taiwan.

In the published sub-analysis of PREFER in AF (PREvention oF thromboembolic events-European Registry in Atrial Fibrillation), the annual risks of thromboembolism and major bleeding for anticoagulated European AF patients aged ≥ 85 years were 4.3% and 4.0%, respectively,[28] which were numerically lower than that of Taiwan AF patients aged 75-89 years with a mean age of 81 years in the present study. These data were consistent to that of the previous report demonstrating that Asian AF patients were associated a higher risk of ischemic stroke and bleeding compared to non-Asians in several pivotal randomized trials comparing NOACs and warfarin.[29]

The use of NOACs are supported by large randomized controlled trials (RCTs) showing clear benefits for NOACs vs warfarin, for efficacy and safety.[6] These RCT data are supplemented by 'real world' post-marketing observational data confirming the effectiveness and safety for NOACs compared to warfarin,[30,31] even in large cohorts from the Far East.[32,33] The present 'real-world' analysis from a nationwide cohort extends these observations in a large nationwide cohort from Asia, particularly showing the safety of NOACs in the very elderly patients. In addition, when compared to warfarin, a clear NOAC benefit for ischemic stroke was evident at age ≥75, while the benefit in relation to ICH, mortality and adverse events was even evident from age ≥65. Given that even the historical randomized trials show a benefit for OAC in reducing stroke (by 64%) and all-cause mortality (by 26%) compared to control or placebo.[34] A lower risk of mortality observed in patients treated with NOACs compared to warfarin even in younger age strata (age 65-74 years) is relevant, notwithstanding the possibility that some deaths in observational cohorts may be fatal strokes since not all outcomes are adjudicated and postmortems are not mandated.

The safety is a major concern for the prescriptions of OACs for the elderly AF population in the daily practice. In the present study, the safety signal in favor of NOACs over warfarin was evident irrespective of age strata, being most marked in the very elderly (age ≥ 90 years) for the risk of ICH. Indeed, the absolute risk difference and reduction of event numbers in ICH and composite adverse events between patients treated with warfarin and NOACs were greatest for the older population. It means that the older the patients, the more benefits the NOACs could provide compared to warfarin. Our findings were similar to that reported from PREFER in AF showing that the absolute benefit of OAC is highest in very elderly patients.[28] In addition to the comparisons between warfarin and NOACs, the annual risk of ischemic stroke, ICH and major bleeding we reported here is also useful for shared decision making with patients.

Study limitations

There are several limitations of the present study. First, information about international normalized ratio and the time in therapeutic range (TTR) for warfarin was lacking in this nationwide registry. In the RE-LY trial, the TTR for warfarin was only 44% in Taiwan.[35] Since a higher TTR is associated with a lower risk of ischemic stroke and ICH for AF patients receiving warfarin, the benefits of NOACs compared to warfarin may be attenuated if the TTR of warfarin could be higher. Second, the present study only enrolled Asian patients, and whether the results can be extrapolated to other populations whose the risk of stroke and ICH may be different remains uncertain. Third, patients with persistent AF had a higher risk of thromboembolic events and worse survival compared with paroxysmal AF in the subanalysis of ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial.[36] Since data about the subtypes of AF were not available from this nationwide dataset, we were not able to know whether types of AF would have impacts on our analysis. Fourth, the data we presented here were based on retrospective analyses of a nationwide cohort, and therefore, some unmeasured confounders and biases (e.g., confounding by indication) may still be present even we have tried to adjust for the differences between patients treated with warfarin and NOACs using the multivariate Cox regression and propensity matching analyses. Owing to this important limitation, we can only report an "association" between the use of NAOCs and the lower risks of clinical events compared to warfarin rather than "causation", and a further prospective and randomized study is necessary to confirm our findings. Lastly, we considered different NOACs as a single group and did not perform separate analysis for each NOAC since these analyses may be even confounded by incidations and doctors' decisions for choosing a particular NOAC. Besides, we only reported types and dosages of NOACs the study population received, and

we were not able to further classify it as appropriate or inappropriate dose since data about body weigth and renal function necessary for the classification were not recorded in our database.

Conclusion

Compared to warfarin, NOACs were associated with a significantly lower risk of adverse events, with heterogeneity in treatment effects among different age strata. Overall, the clear safety signal in favor of NOACs over warfarin was evident irrespective of age strata, being most marked in the most elderly.

Acknowledgments

1. This work was supported in part by grants from the Ministry of Science and Technology (MOST 107-2314-B-075-062-MY3), Taipei Veterans General Hospital (V108B-015, V108B-027, V108C-090), Research Foundation of Cardiovascular Medicine and Szu-Yuan Research Foundation of Internal Medicine, Taipei, Taiwan.

2. This study is based on data from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW), Taiwan. The interpretation and conclusions contained herein do not represent those of HWDC, MOHW, Taiwan.

Author Contributions

Study concept and design: Tze-Fan Chao, Gregory Y. H. Lip, Shih-Ann Chen

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Drafting of the manuscript: Tze-Fan Chao, Gregory Y. H. Lip

Critical revision of the manuscript for important intellectual content: Gregory Y. H. Lip, Shih-Ann Chen

Statistical analysis: Tze-Fan Chao, Jo-Nan Liao

Study supervision: Gregory Y. H. Lip, Shih-Ann Chen

Dr. Tze-Fan Chao, Prof. Gregory Y.H. Lip and Prof. Shih-Ann Chen are guarantors of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

Disclosures

None.

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Table 1. Clinical characteristics of study population

Variables	All (n=64169)	NOACs (n=45632)	Warfarin (n=18537)	P value
Age, mean (SD)	78.54 (7.67)	78.65 (7.44)	78.26 (7.86)	< 0.001
Age ≥ 75 years, n (%)	43568 (67.9)	31462 (68.9)	12106 (65.3)	< 0.001
Age 65-74 years, n (%)	20601 (32.1)	14170 (31.1)	6431 (34.7)	< 0.001
Sex (male), n (%)	34042 (53.1)	24651 (54.0)	9391 (50.7)	< 0.001
Comorbidities, n (%)				
Hypertension	58275 (90.8)	41638 (91.2)	16637 (89.8)	< 0.001
Diabetes mellitus	28925 (45.1)	20517 (45.0)	8408 (45.4)	0.361
Heart failure	36430 (56.8)	24996 (54.8)	11434 (61.7)	< 0.001
Prior stroke/TIA	30383 (47.3)	22452 (49.2)	7931 (42.8)	< 0.001
Vascular disease	10348 (16.1)	6973 (15.3)	3375 (18.2)	< 0.001
COPD	29116 (45.4)	20601 (45.1)	8515 (45.9)	0.069
Hyperlipidemia	37152 (57.9)	26895 (58.9)	10257 (55.3)	< 0.001
Autoimmune diseases	7238 (11.3)	5127 (11.2)	2111 (11.4)	0.580
Cancer	11114 (17.3)	7861 (17.2)	3253 (17.5)	0.330
Abnormal renal function	15059 (23.5)	9505 (20.8)	5554 (30.0)	< 0.001
Abnormal liver function	22274 (34.7)	15914 (34.9)	6360 (34.3)	0.173
Anemia	13605 (21.2)	8736 (19.1)	4869 (26.3)	< 0.001
History of bleeding	27661 (43.1)	19672 (43.1)	7989 (43.1)	0.977
Alcohol excess/abuse, n (%)	560 (0.9)	408 (0.9)	152 (0.8)	0.351
Use of anti-platelet drugs, n (%)	8032 (12.5)	4511 (9.9)	3521 (19.0)	< 0.001
Use of NSAIDs, n (%)	2780 (4.3)	1968 (4.3)	812 (4.4)	0.703
CHA_2DS_2-VASc score, mean (SD)	5.18 (1.67)	5.20 (1.64)	5.15 (1.73)	0.003
HAS-BLED-score, mean (SD)	3.54 (1.23)	3.52 (1.19)	3.59 (1.30)	< 0.001

COPD = chronic obstructive pulmonary disease; NOACs = non-vitamin K antagonist oral anticoagulants; NSAIDs = non-steroidal anti-inflammatory drugs; SD = standard deviation; TIA = transient ischemic attack

Table 2. Clinical characteristics of study patients stratified in different age categories

Variables	Age 65 – 74 years			Age 75 – 89 years			Age ≥ 90 years		
	NOACs (n=14170)	Warfarin (n=6431)	P value	NOACs (n=28179)	Warfarin (n=10609)	P value	NOACs (n=3283)	Warfarin (n=1497)	P value
Age, mean (SD)	69.92 (2.88)	69.61 (2.98)	< 0.001	81.44 (4.11)	81.50 (4.14)	0.200	92.35 (2.46)	92.51 (2.63)	0.430
Age ≥ 75 years, n (%)	-	-	-	28179 (100)	10609 (100)	-	3283 (100)	1497 (100)	-
Age 65-74 years, n (%)	14170 (100)	6431 (100)	-	-	-	-	-	-	-
Sex (male), n (%)	8691 (61.3)	3690 (57.4)	< 0.001	14375 (51.0)	5055 (47.5)	< 0.001	1585 (48.3)	646 (43.2)	0.001
Comorbidities, n (%)									
Hypertension	12554 (88.6)	5384 (83.7)	< 0.001	26004 (92.3)	9833 (92.7)	0.181	3080 (93.8)	1420 (94.9)	0.156
Diabetes mellitus	6601 (46.6)	2863 (44.5)	0.006	12655 (44.9)	4944 (46.6)	0.003	1261 (38.4)	601 (40.1)	0.253
Heart failure	6489 (45.8)	3436 (53.4)	< 0.001	16248 (57.7)	6882 (64.9)	< 0.001	2259 (68.8)	1116 (74.5)	< 0.001
Prior stroke/TIA	6228 (44.0)	2164 (33.6)	< 0.001	14389 (51.1)	5005 (47.2)	< 0.001	1835 (55.9)	762 (50.9)	0.001
Vascular disease	1872 (13.2)	964 (15.0)	0.001	4528 (16.1)	2061 (19.4)	< 0.001	573 (17.5)	350 (23.4)	< 0.001
COPD	4897 (34.6)	2281 (35.5)	0.204	13765 (48.8)	5362 (50.5)	0.003	1939 (59.1)	872 (58.2)	0.597
Hyperlipidemia	9051 (63.9)	3800 (59.1)	< 0.001	16311 (57.9)	5822 (54.9)	< 0.001	1533 (46.7)	635 (42.4)	0.006
Autoimmune diseases	1407 (9.9)	642 (10.0)	0.906	3374 (12.0)	1294 (12.2)	0.548	346 (10.5)	175 (11.7)	0.236
Cancer	1871 (13.2)	909 (14.1)	0.070	5267 (18.7)	2038 (19.2)	0.244	723 (22.0)	306 (20.4)	0.217
Abnormal renal function	2489 (17.6)	1737 (27.0)	< 0.001	6286 (22.3)	3344 (31.5)	< 0.001	730 (22.2)	473 (31.6)	< 0.001
Abnormal liver function	5330 (37.6)	2368 (36.8)	0.276	9657 (34.3)	3579 (33.7)	0.322	927 (28.2)	413 (27.6)	0.643
Anemia	1757 (12.4)	1298 (20.2)	< 0.001	6044 (21.4)	3046 (28.7)	< 0.001	935 (28.5)	525 (35.1)	< 0.001
History of bleeding	5493 (38.8)	2517 (39.1)	0.611	12634 (44.8)	4803 (45.3)	0.440	1545 (47.1)	669 (44.7)	0.127
Alcohol excess/abuse, n (%)	247 (1.7)	96 (1.5)	0.193	197 (0.7)	54 (0.5)	0.558	4 (0.1)	2 (0.1)	0.917
Use of anti-platelet drugs, n (%)	1366 (9.6)	1235 (19.2)	< 0.001	2826 (10.0)	2027 (19.1)	< 0.001	319 (9.7)	259 (17.3)	< 0.001

Use of NSAIDs, n (%)	565 (4.0)	293 (4.6)	0.058	1302 (4.6)	455 (4.3)	0.161	101 (3.1)	64 (4.3)	0.035
CHA_2DS_2-VASc score, mean (SD)	4.21 (1.49)	4.07 (1.55)	< 0.001	5.62 (1.51)	5.70 (1.53)	< 0.001	5.82 (1.45)	5.92 (1.49)	0.038
HAS-BLED-score, mean (SD)	3.35 (1.22)	3.34 (1.37)	0.502	3.59 (1.18)	3.73 (1.25)	< 0.001	3.60 (1.14)	3.70 (1.19)	0.004

COPD = chronic obstructive pulmonary disease; NOACs = non-vitamin K antagonist oral anticoagulants; NSAIDs = non-steroidal anti-inflammatory drugs; SD = standard deviation; TIA = transient ischemic attack

Figure Legends

Figure 1 A flowchart of the enrollment of the study cohort. From January 1, 2012 to December 31, 2015, a total of 64,169 AF patients aged ≥ 65 years who have received at least 1 NOAC (dabigatran, rivaroxaban, or apixaban) or warfarin prescription constituted the study cohort. The risks of ischemic stroke, ICH, major bleeding and mortality were compared between NOACs and warfarin in all patients and those in each age groups; that is 65-74 years, 75-89 years and ≥90 years.

A = apixaban; AF = atrial fibrillation; D = dabigatran; ICH = intra-cranial hemorrhage; NHIRD = National Health Insurance Research Database; NOACs = non-vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants; R = rivaroxaban

Figure 2 Event rate (%/year) in different age strata. The risk of ischemic stroke, ICH, major bleeding, mortality and adverse events increased with increasing age.

CI = confidence interval; ICH = intra-cranial hemorrhage

Figure 3 Risk of events of patients treated with NOACs compared to warfarin. NOACs were associated with a significantly lower risk of ischemic stroke, ICH, major bleeding, mortality and adverse events compared to warfarin, with heterogeneity in treatment effects among different age strata. Overall, the clear safety signal in favor of NOACs over warfarin was evident irrespective of age strata, being most marked in the elderly.

*HRs were adjusted for the variables whose p values were < 0.05 between warfarin and NOAC groups listed in Table 1 for overall comparisons and Table 2 for comparisons in different age strata.

CI = confidence interval; ICH = intra-cranial hemorrhage; HR = hazard ratio; NOACs = non-vitamin K antagonist oral anticoagulants

Figure 4 Cumulative incidence curves of clinical events. Older patients were at higher risks of ischemic stroke, ICH, major bleeding and mortality, with generally better benefits with NOACs versus warfarin. Most importantly, the risk of ICH was even lower for the very elderly patients treated with NOACs compared to younger patients treated with warfarin.

ICH = intra-cranial hemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants

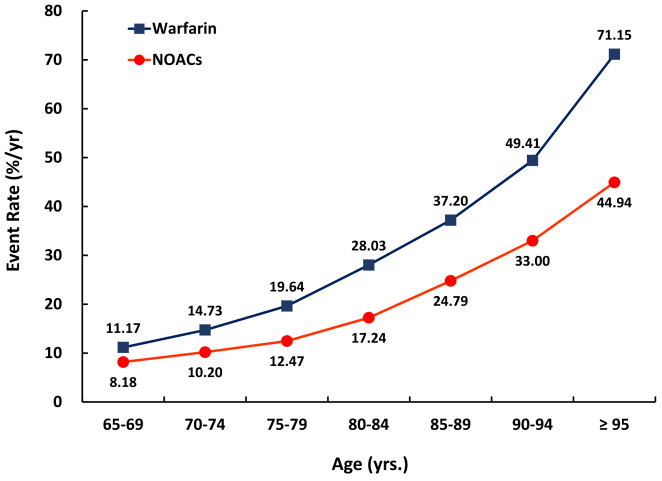
Figure 5 Annual risk of ICH (A) and event reduction with NOACs compared to warfarin (B). The absolute risk difference of ICH between warfarin and NOACs was even more evident in the elderly (Figure 5A). Also, the ICH event reduction (per 1000 patient-years) with NOACs compared to warfarin was even larger among the elderly (Figure 5B).

CI = confidence interval; ICH = intra-cranial hemorrhage; NOACs = non-vitamin K antagonist oral anticoagulants

Figure 6 Annual risk of adverse events (A) and event reduction with NOACs compared to warfarin (B). The absolute risk difference (Figure 6A) and risk reduction (per 100 patient-years) of composite adverse events with NOACs compared to warfarin (Figure 6B) were even larger among the elderly.

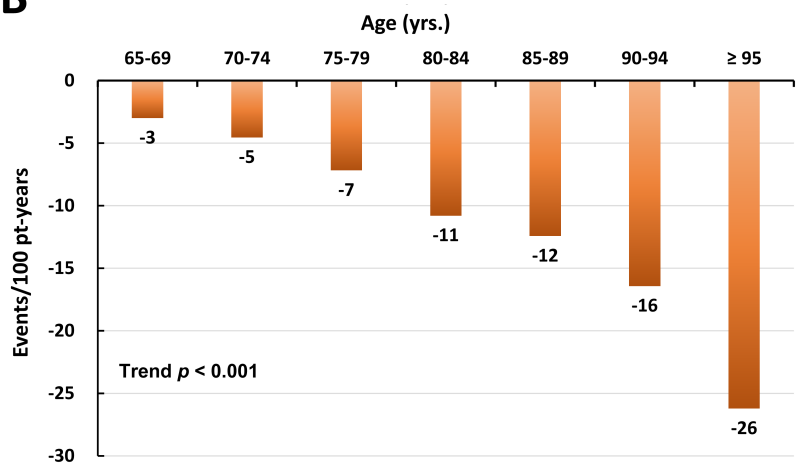
CI = confidence interval; NOACs = non-vitamin K antagonist oral anticoagulants

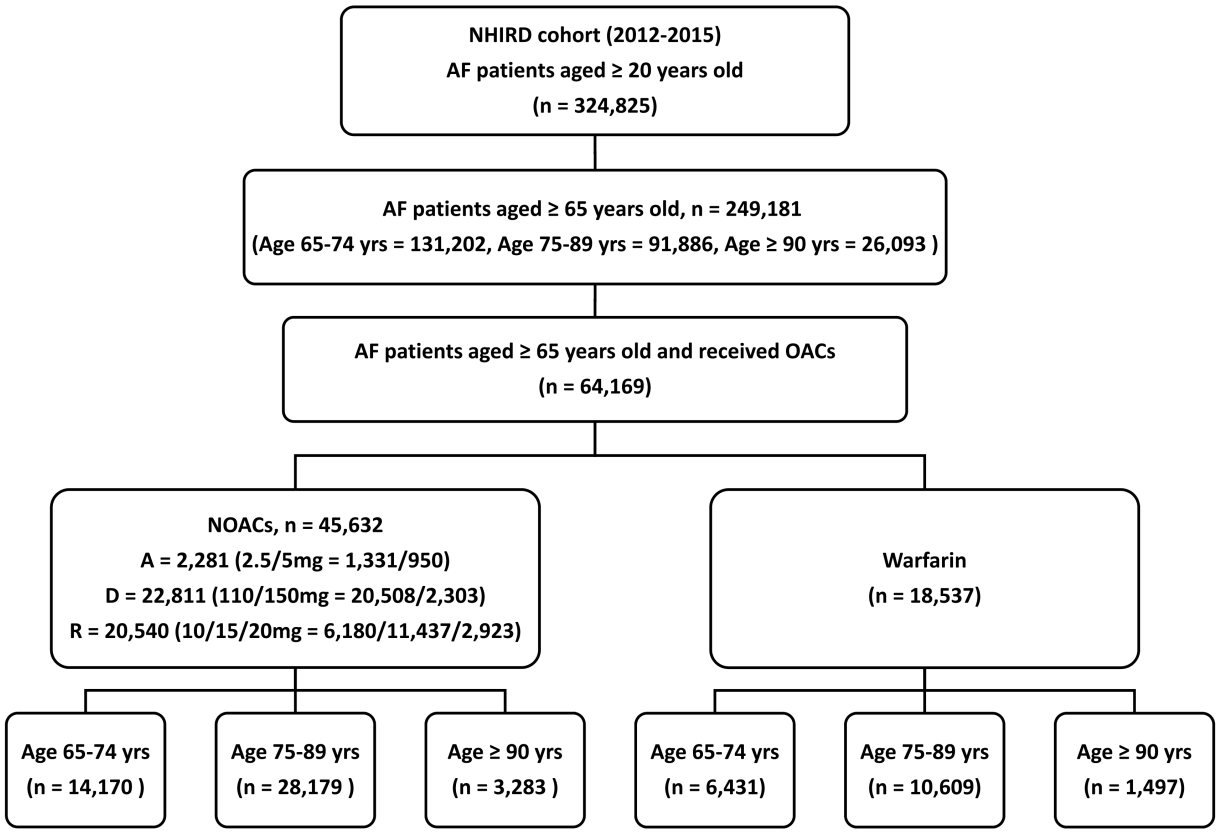
A

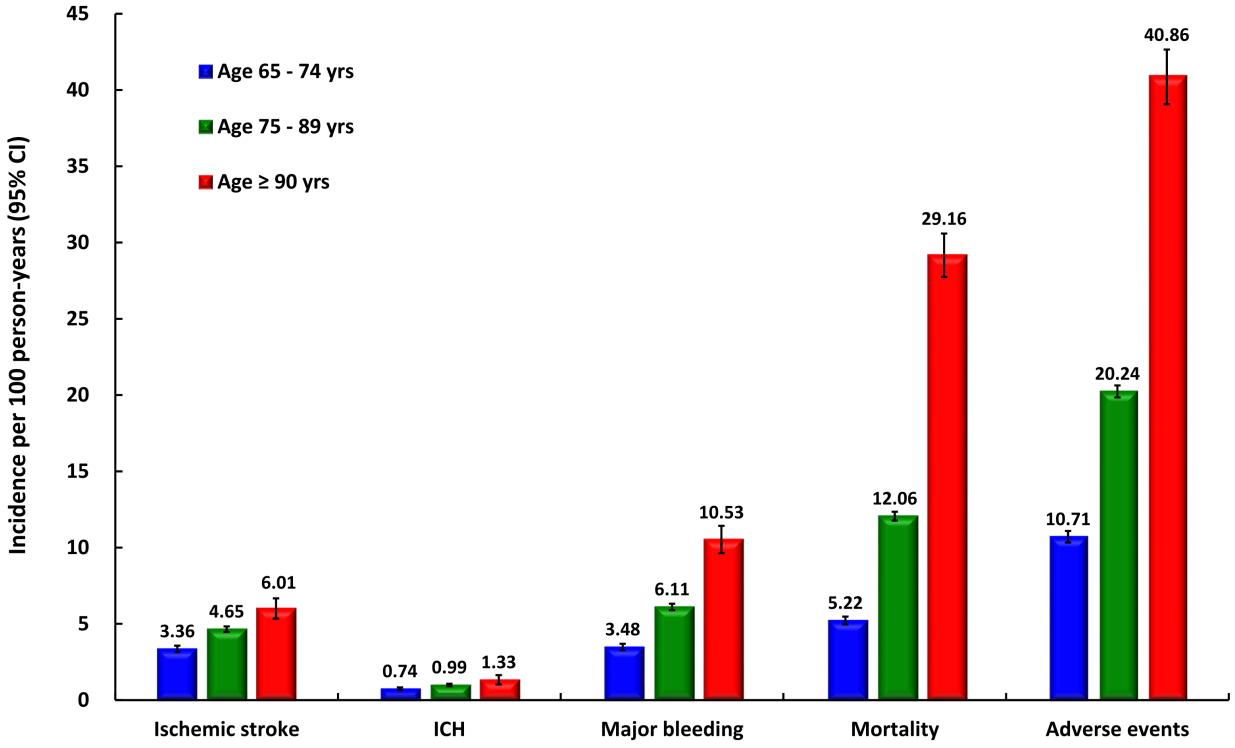


Warfarin	Upper CI	12.10	15.74	20.76	29.44	39.13	53.15	81.29
	Rate	11.17	14.73	19.64	28.03	37.20	49.41	71.15
	Lower CI	10.23	13.72	18.53	26.62	35.27	45.68	61.00
NOACs	Upper CI	8.83	10.81	13.07	17.96	25.83	35.14	50.97
	Rate	8.18	10.20	12.47	17.24	24.79	33.00	44.94
	Lower CI	7.54	9.59	11.88	16.52	23.74	30.86	38.90

B




NHIRD cohort (2012-2015)
AF patients aged ≥ 20 years old
(n = 324,825)
AF patients aged ≥ 65 years old, n = 249,181
(Age 65-74 yrs = 131,202, Age 75-89 yrs = 91,886, Age ≥ 90 yrs = 26,093)
AF patients aged ≥ 65 years old and received OACs
(n = 64,169)
NOACs, n = 45,632
A = 2,281 (2.5/5mg = 1,331/950)
D = 22,811 (110/150mg = 20,508/2,303)
R = 20,540 (10/15/20mg = 6,180/11,437/2,923)
Warfarin
(n = 18,537)
Age 65-74 yrs
(n = 14,170)
Age 75-89 yrs
(n = 28,179)
Age ≥ 90 yrs
(n = 3,283)
Age 65-74 yrs
(n = 6,431)
Age 75-89 yrs
(n = 10,609)
Age ≥ 90 yrs
(n = 1,497)



	Event number (%/yr)					
	Warfarin	NOACs	HR* (95% CI)	NOACs vs Warfarin	P value	Interaction P
Ischemic stroke						< 0.001
All	1,315 (4.53)	2,458 (4.19)	0.869 (0.812 – 0.931)		< 0.001	
Age 65 - 74 yrs	353 (3.25)	636 (3.43)	0.951 (0.832 – 1.087)		0.462	
Age 75 - 89 yrs	848 (5.17)	1,620 (4.42)	0.825 (0.758 – 0.897)		< 0.001	
Age ≥ 90 yrs	114 (6.44)	202 (5.79)	0.899 (0.712 – 1.134)		0.368	
ICH						< 0.001
All	401 (1.33)	439 (0.73)	0.524 (0.456 – 0.601)		< 0.001	
Age 65 - 74 yrs	118 (1.05)	107 (0.56)	0.483 (0.370 – 0.632)		< 0.001	
Age 75 - 89 yrs	242 (1.42)	301 (0.80)	0.564 (0.474 – 0.670)		< 0.001	
Age ≥ 90 yrs	41 (2.26)	31 (0.86)	0.362 (0.226 – 0.580)		< 0.001	
Major bleeding						< 0.001
All	1,736 (6.06)	3,011 (5.19)	0.824 (0.776 – 0.875)		< 0.001	
Age 65 - 74 yrs	435 (4.02)	589 (3.17)	0.779 (0.686 – 0.884)		< 0.001	
Age 75 - 89 yrs	1,103 (6.84)	2,089 (5.79)	0.857 (0.796 – 0.923)		< 0.001	
Age ≥ 90 yrs	198 (11.71)	333 (9.94)	0.862 (0.721 – 1.030)		0.102	
Mortality						< 0.001
All	4,794 (15.77)	5,056 (8.32)	0.511 (0.491 – 0.532)		< 0.001	
Age 65 - 74 yrs	863 (7.63)	728 (3.80)	0.483 (0.436 – 0.534)		< 0.001	
Age 75 - 89 yrs	3,172 (18.39)	3,493 (9.19)	0.504 (0.480 – 0.529)		< 0.001	
Age ≥ 90 yrs	759 (41.18)	835 (23.04)	0.576 (0.521 – 0.636)		< 0.001	
Adverse events						< 0.001
All	6,382 (23.24)	8,836 (15.73)	0.646 (0.625 – 0.667)		< 0.001	
Age 65 - 74	1,364 (13.06)	1,688 (9.35)	0.682 (0.634 – 0.733)		< 0.001	
Age 75 - 89	4,155 (26.99)	6,022 (17.27)	0.636 (0.611 – 0.662)		< 0.001	
Age ≥ 90	863 (52.96)	1,126 (34.78)	0.668 (0.611 – 0.731)		< 0.001	

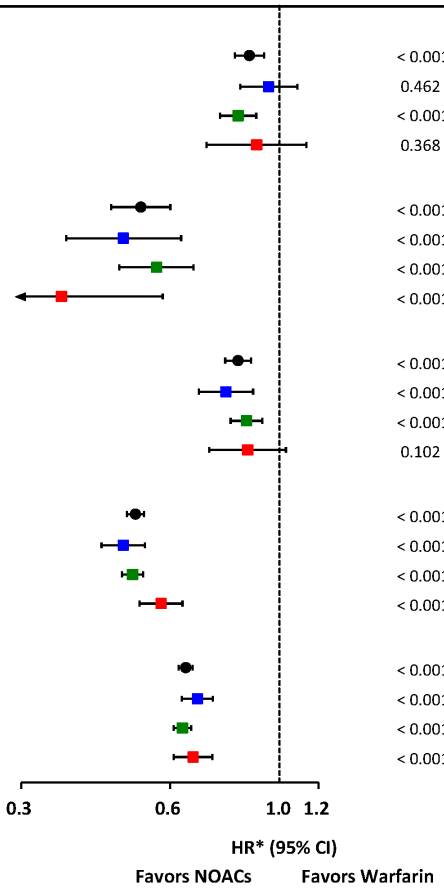
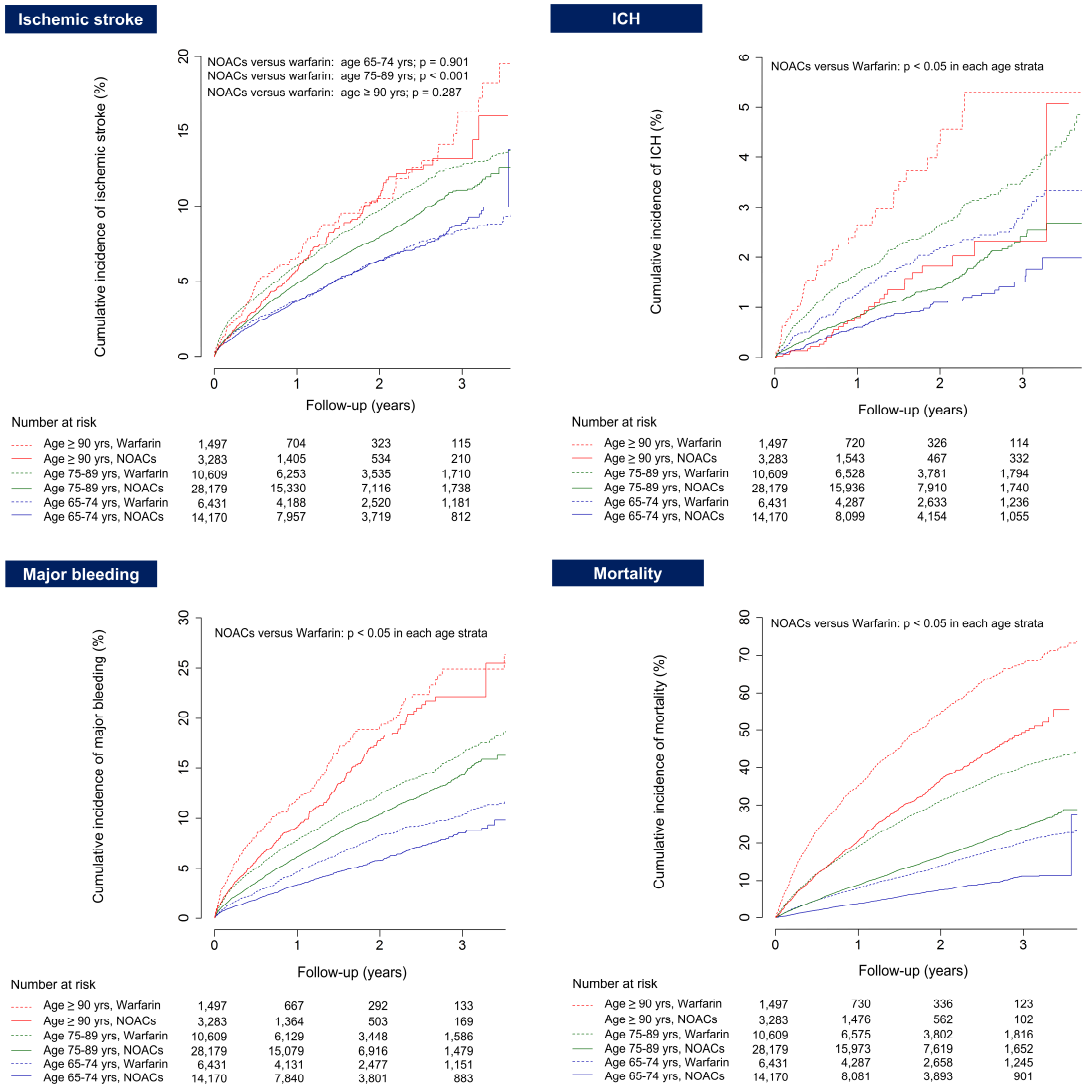
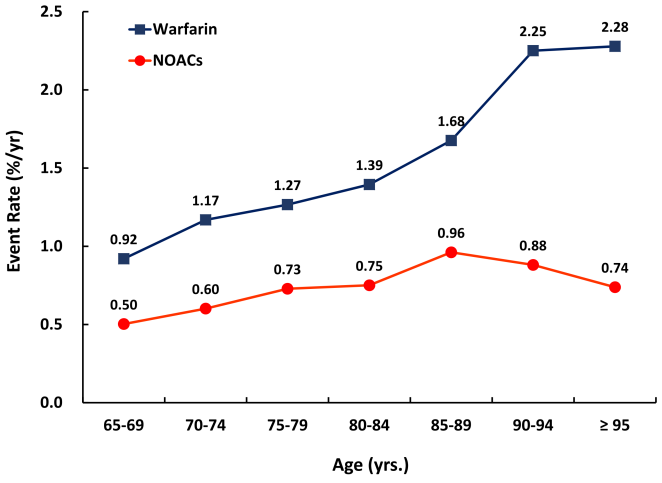


Figure 4


Ischemic stroke
Cumulative incidence of ischemic stroke (%)
NOACs versus warfarin: age 65-74 yrs; p = 0.901
NOACs versus warfarin: age 75-89 yrs; p < 0.001
NOACs versus warfarin: age ≥ 90 yrs; p = 0.287
Follow-up (years)
Number at risk
Age ≥ 90 yrs, Warfarin 1,497 704 323 115
Age ≥ 90 yrs, NOACs 3,283 1,405 534 210
Age 75-89 yrs, Warfarin 10,609 6,253 3,535 1,710
Age 75-89 yrs, NOACs 28,179 15,330 7,116 1,738
Age 65-74 yrs, Warfarin 6,431 4,188 2,520 1,181
Age 65-74 yrs, NOACs 14,170 7,957 3,719 812
ICH
Cumulative incidence of ICH (%)
NOACs versus Warfarin: p < 0.05 in each age strata
Follow-up (years)
Number at risk
Age ≥ 90 yrs, Warfarin 1,497 720 326 114
Age ≥ 90 yrs, NOACs 3,283 1,543 467 332
Age 75-89 yrs, Warfarin 10,609 6,528 3,781 1,794
Age 75-89 yrs, NOACs 28,179 15,936 7,910 1,740
Age 65-74 yrs, Warfarin 6,431 4,287 2,633 1,236
Age 65-74 yrs, NOACs 14,170 8,099 4,154 1,055
Major bleeding
Cumulative incidence of major bleeding (%)
NOACs versus Warfarin: p < 0.05 in each age strata
Follow-up (years)
Number at risk
Age ≥ 90 yrs, Warfarin 1,497 667 292 133
Age ≥ 90 yrs, NOACs 3,283 1,364 503 169
Age 75-89 yrs, Warfarin 10,609 6,129 3,448 1,586
Age 75-89 yrs, NOACs 28,179 15,079 6,916 1,479
Age 65-74 yrs, Warfarin 6,431 4,131 2,477 1,151
Age 65-74 yrs, NOACs 14,170 7,840 3,801 883
Mortality
Cumulative incidence of mortality (%)
NOACs versus Warfarin: p < 0.05 in each age strata
Follow-up (years)
Number at risk
Age ≥ 90 yrs, Warfarin 1,497 730 336 123
Age ≥ 90 yrs, NOACs 3,283 1,476 562 102
Age 75-89 yrs, Warfarin 10,609 6,575 3,802 1,816
Age 75-89 yrs, NOACs 28,179 15,973 7,619 1,652
Age 65-74 yrs, Warfarin 6,431 4,287 2,658 1,245
Age 65-74 yrs, NOACs 14,170 8,081 3,893 901

A



		65-69	70-74	75-79	80-84	85-89	90-94	≥ 95
Warfarin	Upper CI	1.18	1.44	1.54	1.69	2.06	3.01	3.97
	Rate	0.92	1.17	1.27	1.39	1.68	2.25	2.28
	Lower CI	0.66	0.90	1.00	1.10	1.29	1.49	0.59
NOACs	Upper CI	0.66	0.75	0.87	0.90	1.16	1.21	1.46
	Rate	0.50	0.60	0.73	0.75	0.96	0.88	0.74
	Lower CI	0.35	0.46	0.59	0.61	0.77	0.55	0.01

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